Predicting the time course of haemoglobin in children treated with erythropoietin for renal anaemia

R. E. Port,¹ R. W. Ding,^{2,3} T. Fies^{2,4} & K. Schärer^{2,4}

¹German Cancer Research Center and ²University Medical Hospital, Divisions of ³Clinical Pharmacology and ⁴Pediatric Nephrology, D-69120 Heidelberg, Germany

Aims To establish a pharmacodynamic model that allows one to predict the haemoglobin (Hb) response to EPO in children as a function of dose and time, and to derive recommendations for initial dosing and subsequent dose adjustment.

Methods Haemoglobin was monitored in eight children aged 8–15 years with anaemia due to renal failure during treatment with EPO. All patients were free of conditions known to impair the response to EPO. Pretreatment Hb was 4.9–9.0 g dl⁻¹. The drug was administered once weekly by subcutaneous injection; doses ranged from 1700 to 6800 U week⁻¹. Hb was monitored for 4–38 months. The Hb-time data were analysed by applying a population pharmacodynamic model proposed for EPO in adult haemodialysis patients [1]. Internal model validation was carried out by using a bootstrap procedure.

Results The increase of Hb during treatment with EPO was linear until steady state was reached after 103 ± 33 days (mean ± interindividual s.d.). The weekly gain in Hb from the onset of therapy to steady state was 0.0805 ± 0.026 g dl⁻¹ (mean ± interindividual s.d.) for every 1000 U EPO week⁻¹; it did not exhibit a dependence on body weight. Estimated mean prediction errors are ± 1.53 g dl⁻¹ for predictions that are based on the mean population parameters and ± 0.83 g dl⁻¹ for predictions that take into account the complete individual Hb-time data up to and including steady state.

Conclusions The model describes the time course of the Hb response to EPO in children with renal anaemia. The required weekly EPO dose should initially be calculated from the individual pretreatment Hb and the desired Hb at steady state by using the mean population estimates of the weekly gain in Hb per dose unit before steady state (β) and the time needed to reach steady state (τ). A reduction of the initial dose according to body weight is not justified by the available evidence. β should be re-estimated individually after 6 weeks of treatment and dose should be adjusted accordingly. A final dose adjustment should be made when steady state has been reached based on individual estimates of β and τ .

Keywords: haemoglobin, NONMEM, pharmacodynamics, population analysis

Introduction

Administration of recombinant human erythropoietin has become standard treatment for renal anaemia in children [2, 3] as well as in adults [4]. The effect on haemoglobin (Hb) concentration in blood is fairly predictable provided that bone marrow function or the expression of response are not compromised by conditions other than renal failure such as hyperparathyroidism, infections, or insufficient iron supply.

Pharmacodynamic modelling has been applied to the Hb-time data of adult haemodialysis patients treated with EPO [1, 5]. Both of these studies independently lead to the conclusion that, on average, each 1000 U of EPO induces an increase in Hb of 0.04 g dl⁻¹ which lasts for about 70 days. This timespan was interpreted as the lifespan of the

drug-induced erythrocytes. Notably, this dose–response relationship was found for dose expressed as absolute amount, not as units per kg body weight. A qualitatively similar observation has been made in children with end-stage renal disease: The maintenance dose required for the management of anaemia, when expressed in units per kg body weight, was higher in small children than in older children [2].

The population pharmacodynamic model proposed for adults by Uehlinger *et al.* [1], allows one to estimate the weekly rise of Hb for a given constant EPO dosage, the time it will take to reach steady state, and the interindividual variance of both of these parameters. All of this information together can be used to predict the entire time course of Hb during treatment and to determine individual dosage in a more rational way than by starting with a uniform dose per unit body weight and adjusting dose based on observed Hbs at arbitrary time points [1].

Correspondence: Dr R. E. Port, German Cancer Research Centre, D-69129 Heidelberg, Germany.

The aim of the present study was to estimate the population parameters of the Hb-time course in children treated with EPO by applying the model of Uehlinger *et al.* [1] and to determine whether in children, too, response is related to absolute dose rather than to dose per unit body weight.

Methods

Subjects and treatment

A group of eight children aged 7–15 years with renal anaemia were chosen for investigation (Table 1). Patients were selected for study if they were followed for at least 8 weeks after the beginning of EPO treatment, if they complied with oral iron medication, and if they had no blood transfusions during the period of observation. All patients were free of concomitant conditions expected to impair response to EPO such as peritonitis, hyperparathyroidism, oxalosis, splenomegaly, or familial mediterranean fever. A single febrile episode due to peritonitis occurred in patient 6.

EPO was administered once weekly as a buffered solution (Cilag, Sulzbach, Germany). The initial dose was 100–170 U week⁻¹ kg⁻¹; individual dosing *vs* time is shown in Figure 1.

Pharmacodynamic and statistical analysis

The dose-time-Hb data of all patients were analysed simultaneously using the population model proposed by

Uehlinger *et al.* [1] for adult haemodialysis patients (model A3/A4). We refer the reader to [6] for a review on the population modelling approach. Briefly, this model assumes that a constant number of red blood cells is induced by the drug each day as long as EPO is given at constant intervals (e.g. once weekly). As a result, Hb rises at a constant rate from the time treatment has been initiated. All drug-induced red cells within an individual are assumed to have the same lifespan. After the lifespan of the first drug-induced cells has ended, the number of cells dying each day will equal the number of cells that are induced each day so that Hb is at steady state. When treatment is stopped Hb starts to decline at a constant rate until it is back to pretreatment level; the rate of decline is the same as the rate of initial rise. The effect of changing dosage can be modelled by assuming that one treatment was stopped and another one was initiated, and by adding the effect of both treatments. The time to steady state, the time until the full effect of a dosage change is apparent, and the duration of decline of Hb after discontinuation of treatment are all equal to the lifespan of the drug-induced red cells under this model. The rate of drug-induced Hb production (which adds to the spontaneous production rate) is assumed to be linearly related to the EPO dose applied:

$$R = \beta \cdot D \quad (1)$$

where R is drug-induced Hb production rate (g dl⁻¹ week⁻¹), β is production rate per dose unit (g dl⁻¹ week⁻¹/(U week⁻¹)), and D is dose (U week⁻¹). β may be called a 'responsiveness' parameter and is assumed to vary randomly between individuals; similarly, the red blood cell

Table 1 Clinical and laboratory data.

Patient number	Gender	Age (Years)	Weight (kg) at start of EPO treatment	Height (cm)	Basic disease	Therapy ¹
1	M	7.6	17.0	111.2	obstructive uropathy	PD
2	M	8.3	17.7	114.3	glomerulonephritis	PD
3	M	10.3	30.0	140.4	obstructive uropathy	CT
4	F	10.9	26.0	130.2	nephronophthisis	CT
5	F	12.2	29.8	132.0	glomerulonephritis	PD
6	F	12.8	36.0	157.8	immunovascularitis	PD
7	F	13.4	25.0	132.5	glomerulonephritis	PD
8	M	14.7	58.6	178.0	multicystic renal dysplasia	PD

¹PD: peritoneal dialysis, CT: conservative treatment

Patient number	Time on EPO treatment (weeks)	Weight gain (kg)	Hb at start of EPO (g dl ⁻¹)	Hb at end of EPO (g dl ⁻¹)	β_i ((g dl ⁻¹ week ⁻¹)/ (1000 U week ⁻¹))	τ_i (days)
1	56	2.5	6.8	9.8	0.085	113
2	36	1.0	4.9	10.5	0.089	156
3	165	12.2	5.9	10.7	0.058	162
4	41	2.2	9.0	11.5	0.131	87
5	33	0.4	6.9	10.5	0.122	89
6	43	1.3	6.3	9.9	0.055	139
7	50	3.8	5.2	9.0	0.077	85
8	16	-3.8	7.2	11.2	0.060	105

Figure 1 Individual time courses of haemoglobin concentration in peripheral blood (Hb; left ordinate) and of dose of EPO applied per week (right ordinate). Each point represents one Hb measurement. Thick solid curve: 'fixed-effects predictions' derived from one pretreatment measurement and the mean population parameters $\bar{\beta}$ and $\bar{\tau}$. Dotted curve: 'mixed-effects predictions' based on empirical Bayes estimates of individual baseline Hb and β . Thin solid curves at bottom of chart: EPO dose.

lifespan, τ , is assumed to vary randomly between individuals:

$$\beta_i = \bar{\beta} \cdot e^{\eta_{1i}} \quad (2)$$

$$\tau_i = \bar{\tau} \cdot e^{\eta_{2i}} \quad (3)$$

where β_i and τ_i are the β and τ parameters of individual i ($i=1, \dots$, number of individuals), $\bar{\beta}$ and $\bar{\tau}$ are the corresponding population means, and η_1 and η_2 are random variables with mean zero, variances ω_1^2 and ω_2^2 , respectively, and no covariance. Residual error was assumed to be additive:

$$Hb_{ij} = \hat{H}b_{ij} + \varepsilon_{ij} \quad (4)$$

where Hb_{ij} is Hb observed in individual i at time j ($j=1, \dots$, number of observations in individual i), $\hat{H}b_{ij}$ is the

sum of the individual baseline Hb and the effect of treatment as predicted from dose, time, and the individual β_i and τ_i parameters, and ε has mean zero and variance σ^2 . Individual baseline Hbs were estimated based on pretreatment measurements and overall residual variance as follows: One pretreatment measurement was available in each individual which was assumed to deviate randomly from true individual baseline level:

$$Hb_{i0} = bl_i + \tau_{3i} \quad (5)$$

where Hb_{i0} is the pretreatment Hb measurement of individual i , bl_i is true individual baseline Hb, and τ_3 varies randomly between individuals with mean zero and variance

ω_3^2 . Rearrangement gives:

$$bl_i = Hb_{i0} - \tau_{i3} \quad (6)$$

This relationship was used to estimate individual baseline levels by assuming that ω_3^2 is equal to the overall residual variance, σ^2 [7].

Internal validation of the final model was carried out using a bootstrap procedure [8] as recently applied to population pharmacokinetic data [9]. Briefly, random samples of eight patients were drawn with replacement from the original data set. The final model was fitted to each of the random sample data sets and mean squared prediction errors were calculated for fixed-effects predictions: AE_{boot}^{fep} , and for mixed-effects predictions: AE_{boot}^{mep} . The parameters fitted to the random sample data set were then used to make fixed-effects predictions and (Bayesian) mixed-effects predictions for the data of the original data set. Again, mean squared prediction errors were calculated for fixed-effects predictions: PE_{orig}^{fep} , and for mixed-effects predictions: PE_{orig}^{mep} . Subtracting AE_{boot} from PE_{orig} gives an estimate of the 'optimism', opt , implied in 'naively' estimating prediction errors, PE_{naive} based solely on fitting the model to the original data set:

$$opt^{fep} = PE_{orig}^{fep} - AE_{boot}^{fep} \quad (7)$$

$$opt^{mep} = PE_{orig}^{mep} - AE_{boot}^{mep} \quad (8)$$

Adding the estimated optimism, opt , to PE_{naive} gives an improved estimate of the average squared prediction error, PE_{imp} :

$$PE_{imp}^{fep} = PE_{naive}^{fep} + opt^{fep} \quad (9)$$

$$PE_{imp}^{mep} = PE_{naive}^{mep} + opt^{mep} \quad (10)$$

The program system NONMEM, version IV [10], with the 'Laplacian' conditional estimation method was used for model fitting. Additional model parameters were tested for their improving the goodness of fit using the likelihood ratio criterion [11] with $\alpha < 0.05$.

Results

All eight patients studied responded to treatment with an Hb increase ranging between 2.5 and 5.6 (median: 3.7) g dl^{-1} from the beginning to the end of EPO treatment (Table 1, Figure 1). The optimum model to describe the Hb-time course in response to EPO includes the population means of β and τ , their interindividual variances, ω_1^2 and ω_2^2 , and the residual variance σ^2 as its only parameters. Describing the dose-response relationship by an $E_{\max}$ model did not improve the fit significantly. The data suggest a decrease of τ with age but this trend cannot be verified statistically. Our estimate of β (population mean $\pm$ interindividual standard deviation) is $0.0805 \pm 0.026 \text{ g dl}^{-1} \text{ week}^{-1}/(1000 \text{ U week}^{-1})$; the corresponding estimate for τ is 103 ± 33 days.

'Fixed-effects predictions', i.e. predictions of Hb *vs* time based on one measurement immediately before the onset of EPO treatment and on the mean population parameters $\bar{\beta}$ and $\bar{\tau}$, are shown for each patient in Figure 1 as solid lines. Empirical Bayes estimates of the individual parameters bl_i , β_i , and τ_i were obtained based on the population parameters,

Figure 2 (a) Individual responsiveness parameter (β_i : drug-induced Hb production rate ($\text{g dl}^{-1}/\text{week}^{-1}$ per 1000 units EPO week^{-1}) *vs* body weight. (b) Hb observed – Hb predicted *vs* body weight. Except for the first measurement in each individual, the data are equivalent to change (Δ) in Hb observed – Δ in Hb predicted; predicted values are based on absolute doses.

$\bar{\beta}$, $\bar{\tau}$, ω_1^2 , ω_2^2 , σ^2 and each individual's complete set of Hb measurements by using NONMEM's POSTHOC function [10] (Table 1). These estimates are the most likely values of the individual parameters given the population mean and variance parameters and the individual observations. 'Mixed-effects predictions' based on these individual parameters are shown in Figure 1 as dotted lines. Typical prediction error (computed as the square root of mean $(Hb_{ij} - \hat{Hb}_{ij})^2$) was $\pm 1.43 \text{ g dl}^{-1}$ for fixed-effects predictions (Figure 1, thick solid curves) and $\pm 0.80 \text{ g dl}^{-1}$ for mixed-effects predictions (Figure 1, dotted curves). Mixed-effects predictions which only use Hb measurements up to 4, 6, 8, 10, or 12 weeks of treatment had mean prediction errors between 1.13 and 1.27 g dl^{-1} .

Individual drug-induced Hb production rate per dose unit (β_i) does not show a consistent trend to decrease with body weight (Figure 2a). Note that in Figure 2(a) dose has been expressed in absolute terms (U week^{-1}) and has not been related to body weight. Likewise, a plot of residuals (Hb observed minus Hb predicted from the mean population parameters) *vs* body weight does not show a trend towards more negative residuals with increasing body weight. This plot (except for the first observation in each individual) is equivalent to showing observed minus predicted change in Hb (Δ). The observed Δ s are neither particularly high in small children nor particularly low in large patients even though they are related to a prediction which is based on absolute dose.

Internal validation by fitting the model to 200 bootstrap sample data sets resulted in improved estimates of typical prediction errors of $\pm 1.53 \text{ g dl}^{-1}$ for fixed-effects predic-

tions and $\pm 0.83 \text{ g dl}^{-1}$ for mixed-effects predictions. The means of the bootstrap parameter estimates were within 2% of the original parameter estimates, except for $\bar{\tau}$ (+14%) and ω_2^2 (-25%). The coefficients of variation of the bootstrap parameter estimates were less than 20% for $\bar{\beta}$ and $\bar{\tau}$, and were 48 and 77% for ω_1^2 and ω_2^2 , respectively.

Discussion

The population parameters presented allow one to make predictions of the time course of Hb in children with renal anaemia who have an initial treatment with EPO provided that bone marrow function is not compromised by factors other than uraemia. The concept that Hb rises at a constant rate until steady state is reached appears to be applicable in children as well as in adults [1]. Internal validation of our results by using a bootstrap procedure shows large coefficients of variation for the interindividual variance estimates; these are probably due to the small size of our patient group. Even though renal failure under long-term observation is relatively rare in children more patients should be investigated for their Hb-time course under EPO treatment in order to improve on the precision and possibly the accuracy of the present population parameter estimates. Additional data should include a wider range of ages and the hypothesis of a dependence of τ on age should be reevaluated. Predictions based on the present results refer to doses between 1700 and 6800 U week⁻¹. Little benefit has been seen in adults from increasing the dose beyond 6800 U week⁻¹ [1].

'Fixed-effects predictions' can be made based on one or more Hb measurements taken shortly before the onset of EPO treatment, and on the mean population parameters $\bar{\beta}$ and $\bar{\tau}$. Calculations are simple because it is assumed that drug-induced Hb production rate is proportional to the weekly dose over the entire observation period. As an example, consider patient 3 (Figure 1) who had a pretreatment Hb of 5.9 g dl^{-1} and, for the first 15 months, received 4500 U EPO week⁻¹. The initial rise of Hb to be expected is $4.5 \cdot 0.0805 \text{ g dl}^{-1} \text{ week}^{-1} = 0.36 \text{ g dl}^{-1} \text{ week}^{-1}$ (weekly dose, expressed in multiples of 1000 U, times $\bar{\beta}$). The expected steady state Hb is $5.9 \text{ g dl}^{-1} + 0.36 \text{ g dl}^{-1} \text{ week}^{-1} \cdot 15 \text{ weeks}$ (baseline Hb plus weekly rise of Hb times $\bar{\tau}$). This prediction can be improved after 6 weeks of treatment by estimating the individual random deviations of true baseline Hb (bl_i) from measured pretreatment Hb, and of individual responsiveness (β_i) from the mean population responsiveness ($\bar{\beta}$). (NONMEM's 'POSTHOC' function can be used to obtain these estimates.) The resulting 'mixed-effects predictions' (after 6 weeks of treatment) had a mean prediction error of 1.13 g dl^{-1} in our patients; this compares with 1.43 g dl^{-1} for the 'fixed-effects predictions' made at the beginning of treatment. No further improvement of predictions was achieved by using the individual observations up to 16 weeks of treatment. A rational dosing strategy for clinicians would be to calculate the required initial EPO dose from pretreatment Hb and desired steady state level by using the population estimates of mean responsiveness ($\bar{\beta}$) and mean red cell lifespan ($\bar{\tau}$). More than one Hb measurement may be taken shortly before the onset of treatment in order to improve the initial estimate of

pretreatment Hb. The dose should be adjusted after 6 weeks of treatment based on individual estimates of baseline Hb and responsiveness which take into account the individual Hb measurements accrued up to this time point.

The full effect of a given dose will be apparent only when steady state has been reached. Only then a final dose adjustment can be made which takes into account the individual time to steady state (τ_i). Individual steady state Hb may substantially differ from what was predicted after 6 weeks of treatment if τ_i differs much from the estimated population mean of 103 days. An example is patient 3 whose τ_i was 161 days resulting in steady state Hb levels higher than expected based on his fixed-effects predictions (Figure 3, solid line). An example of the opposite situation is provided by patient 7 whose τ_i , 84 days, was too short to reach a satisfying steady state level with the initial dose. If a dose adjustment is made after reaching steady state it will again take a time interval of length τ_i for the effect of dose change to become fully apparent.

The average lifespan of red blood cells in uraemic children has been determined to be 76% of that of healthy adults [12] which is about 120 days [13, 14]. Thus, our estimate of $\bar{\tau}$ roughly corresponds to the average red blood cell lifespan of uraemic children as determined by other methods.

Our data do not show a consistent dependence of Hb response to EPO on body weight for a given absolute dose (Figure 2a,b). Also, the individual plots of dose and Hb *vs* time (Figure 1) indicate that, as a trend, the initial rise of Hb is related to absolute dose irrespective of body weight. This may seem surprising and one might interpret it as a random phenomenon produced in a small sample by the wellknown variability of the response to EPO in uraemic children [3]. However, a linear relationship between absolute dose and response has also been reported for adult haemodialysis patients ranging in weight from 45 to more than 80 kg [1, 5]. A qualitatively similar observation has been made in a multicentre study of children aged 6 months to 20 years: The maintenance dose required for the treatment of renal anaemia, when expressed in units per kg body weight, was about two times higher in small children (<30 kg) than in older children or adolescents (>30 kg) [2]. Thus, the presently available data do not support a reduction of EPO doses according to body weight, at least for body weights down to 20 kg.

The mean response to subcutaneous EPO determined for our pediatric patients with predialysis renal failure or on peritoneal dialysis is about twice that reported for adult haemodialysis patients on intravenous EPO for doses up to 7000 U week⁻¹ ($0.04 \text{ g dl}^{-1} \text{ week}^{-1}$ per 1000 U week⁻¹ assuming an equivalence of 3% haematocrit for 1 g dl^{-1} Hb) [1, 5]. It is not clear whether this difference in response is an age related phenomenon or a result of the different routes of administration as some studies have shown a higher efficacy of subcutaneous *vs* intravenous EPO [15–17].

In conclusion, the time course of Hb response to EPO in children with renal anaemia can be predicted using the same model that has been successfully applied to the data of adult haemodialysis patients [1]. The current practice of standardizing initial dose by body weight should be reevaluated because it is not supported by the results of this study. Initial dose should be calculated from pretreatment

Hb and the desired Hb at steady state by using the estimated population means of responsiveness (β) and red blood cell lifespan (τ). Dose should be adjusted individually after 6 weeks of treatment according to the observed rate of rise of Hb. A final dose adjustment may be made after measured Hb has reached a plateau.

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